REMARKS

Claims 1-19 are pending. Claims 13-19 are withdrawn from consideration. Claims 1-12 are rejected. Amendment to the claim language has been made solely to overcome indefiniteness rejections and to put the claims into acceptable U.S. form. No new matter has been added. Reconsideration is requested.

Rejection under 35 USC §112, second paragraph

Claims 3 and 9 were rejected under 35 USC § 112, second paragraph, as being indefinite. Claim 3 was amended to recite "encoding", as helpfully suggested by the Examiner. Claim 9 has been amended in independent form. It is believed that the claims are free of indefiniteness rejections. Reconsideration and withdrawal thereof are respectfully requested.

Rejection under 35 USC §103

Claims 1-12 were rejected under 35 USC §103(a) as being unpatentable over Ilan et al. in view of DeMatteo et al and further in view of Bakker et al. This rejection is traversed for the following reasons.

With regard to this ground of rejection, the Examiner recites three references, namely (1) Ilan et al. (1996) J. Clin. Invest., Vol. 98 (11), 2640-2647, (2) DeMatteo et al. (1997) J. Virol., Vol. 71 (7), 5330-5335, and (3) Bakker et al. (1999) J. Immunol., Vol. 162, 3456-3462, which are cited in the previous action, and states that the invention of Claims 1-12 is taught by the description of these references.

Applicants respectfully submit that the Examiner has misunderstood the differences between the present invention and that described in the references.

(1) Ilan et al.

Regarding the reference Ilan et al., the Examiner states that "The applicant argues that Ilan et al. does not describe or suggest that immunological tolerance occurs by transferring a foreign DNA into immature T lymphocytes and introducing these cells into thymus. The

applicant further argues that the skilled artisan would not be motivated to follow the method of Ilan because Ilan describes the direct administration of adenovirus to the thymus which could lead to systemic toxicity." Relating to this, the Examiner further states that the office disagrees with the applicant's interpretation of the teaching of Ilan et al. First, Ilan et al. clearly teaches that introduction of foreign antigen into the thymus results in the induction of immunological tolerance to the foreign antigen. Further, Ilan et al. teaches two different methods to introduce the foreign antigen to the thymus. While Ilan et al. does teach the direct administration of recombinant adenovirus, Ilan et al. also clearly teaches the administration of **cells** transduced with the recombinant adenovirus (Ilan et al., page 2640). Specifically, the previous office action stated that Ilan et al. teaches that in mammals pretreated by thymic injection of cells infected with recombinant adenovirus encoding a therapeutic gene such as human BUGT1, a second intrahepatic injection of the recombinant adenovirus resulted in sustained gene expression of at least 7 weeks (Ilan et al., page 2640)". In other words, although the applicant argues that "Ilan et al. describes the direct administration of adenovirus to the thymus," the Examiner disagrees by reciting "While Ilan et al. does teach the direct administration of recombinant adenovirus, Ilan et al. also clearly teaches the administration of cells transduced with the recombinant adenovirus."

Applicants respectfully submit that, as Ilan et al. teaches a method to acquire immunological tolerance for comparatively long time by introducing "hepatocytes with recombinant adenovirus" into thymus, it can be said that the administration using cells is described. However, Ilan et al. neither describes nor teaches transfection of the "immature T lymphocytes" with gene and introduction of the "immature T lymphocytes" into thymus as described in the present invention.

The reference of Ilan et al. is originally cited as a reference of prior art in the specification of the present patent application (J. Clin. Invest. 98, 2640-2647, 1996: page 3, lines 19-22), and what is described in this reference is a conventional method of direct introduction of antigen into thymus. As pointed out by the Examiner, the reference describes a method of integrating genes into "hepatocytes" and introducing the gene into thymus. This method is only supplying antigen

to thymus by expressing the gene in the thymus. Therefore, a method using a cell does not substantially differ from the method of introducing antigen directly into thymus. Meanwhile, Applicants have already shown the defect in carrying out the method of direct introduction of antigen into thymus.

In contrast, the present invention uses the "immature T lymphocytes." In describing the significance (effect) of using the cell, Applicants note that the mechanism of acquiring immunological tolerance is as follows:

1) The thymus is an organ in which the "immature T lymphocytes" are differentiated into mature T lymphocytes. In the process of differentiation of T lymphocytes in thymus where the "immature T lymphocytes" are differentiated into mature T lymphocytes, T lymphocytes which react to molecules expressed in thymus are excluded. Immunological tolerance to the molecule is acquired as the result. In other words, the nature of immune system that shows self-tolerance and reacts to non-self is generally acquired in the process of differentiation of T lymphocytes in thymus.

2) The reason for using the "immature T lymphocytes" in the present invention is to use the mechanism of acquiring immunological tolerance in the process of differentiation of T lymphocytes. In other words, in the present invention, acquired immunological tolerance can be induced by using the above mechanism of acquiring immunological tolerance in the process of differentiation of the "immature T lymphocytes" in thymus, by integrating genes expressing antigen into the "immature T lymphocytes" and introducing the "immature T lymphocytes" into thymus. The main object of the present invention is to induce acquired immunological tolerance in the process of differentiation of the "immature T lymphocytes" in thymus, where not only induction of antigen into thymus via cell but also reconstruction of immune system is performed simultaneously.

The present invention has an excellent practical advantage that acquisition of effective immunological tolerance becomes possible with a natural biological reaction, since the present

invention uses a natural mechanism of acquiring immunological tolerance as stated above.

3) The present invention further has the following advantages by using the "immature T lymphocytes": (i) It is not necessary to inject cells into thymus and it is possible to administer antigen intravenously (procedure of blood transfusion) into thymus safely and simply when introducing antigen into thymus in the present invention, because the "immature T lymphocyte" has a nature of being transfected from circulating blood into thymus, and (ii) The subject cells of the induction of tolerance are T lymphocytes in the body, and as the "immature T lymphocytes" are used as vectors (carriers) of tolerance inducing molecules in the present invention, immunological tolerance can be induced effectively.

As described above, the present invention makes it possible to induce effectively immunological tolerance with a natural biological reaction using the "immature T lymphocytes" and by using a natural mechanism of acquiring immunological tolerance.

Ilan et al. does not describe, teach, or suggest anything about "immature T lymphocytes", and accordingly, does not render the presently claimed invention obvious .

(2) DeMatteo et al.

Regarding this reference, the Examiner states that "The applicant further argues that DeMatteo et al. also teaches the direct administration of adenovirus and presents evidence in the form of post-filing references that systemic administration of adenovirus can cause toxicity. However, Ilan et al. has already been cited as the primary reference teaching the administration of cells transfected with adenovirus to thymus. Thus, as noted above, concerns of systemic toxicity are not relevant. Further, DeMatteo et al. was cited to supplement the teaching of Ilan et al., by teaching that adenovirus is capable of infecting fetal T lymphocytes in fetal thymus and further that the transduced fetal T lymphocytes induce tolerance (DeMatteo et al., page 5330, abstract, and Figure 1). It is also noted that DeMatteo et al. teaches that by using a cellular carrier to prevent viral extravasation into the periphery, adverse systemic reactions to adenovirus can be avoided (DeMatteo et al., page 5334, column 2)."

In other words, the Examiner states that the applicant argues that DeMatteo et al. teaches the direct administration of adenovirus but the administration of cells transfected with adenovirus into thymus is also taught both in aforementioned Ilan et al., and in DeMatteo et al., page 5334, column 2.

Applicants respectfully submit that there is neither description about the "immature T lymphocytes" nor description indicating it in DeMatteo et al., as it was the case in above Ilan et al. Though Ilan et al. has already been cited as major reference, as described above, there is neither description nor suggestion about the "immature T lymphocytes" in Ilan et al. Therefore, we presume that the present invention is not taught from the description even by combining the description of the two references.

(3) Bakker et al.

The Examiner states that "Regarding the teaching of Bakker et al., the applicant argues that Bakker et al. does not teach that fetal thymocytes infected with adenovirus can induce tolerance. In response, Bakker et al. was cited to further supplements Ilan et al. and DeMatteo et al. by teaching methods of infecting fetal T lymphocytes with recombinant adenovirus *in vitro* in fatal thymic organ culture (Bakker et al., page 3457). Bakker et al. further teaches that fetal thymocytes infected with adenovirus develop into single positive mature T lymphocytes which ultimately migrate to the periphery (Bakker et al., page 3458, Figure 1, and page 3456). The requisite teachings of the induction of tolerance are provided by Ilan et al., and supplemented by DeMatteo et al."

Applicants respectfully submit that, as Bakker et al. only describes "fetal thymocytes infected with adenovirus containing mut-IκB", there is no rational ground to combine this description with those of Ilan et al. and DeMatteo et al. It appears that the examiner has used hindsight to combine the references, an impermissible basis for making an obviousness rejection. Furthermore, even if the references are combined, it would not lead to the presently claimed invention, a method which requires that an immature T lymphocyte transfected with the foreign DNA be introduced into thymus.

Conclusion

As stated above, even when the descriptions of Bakker et al., DeMatteo et al., and Ilan et al., are considered together, the present invention is not taught by the combination. Therefore, it is respectfully requested that the rejection of claims 1-12 under 35 U.S.C.103 (a) as being unpatentable over Ilan et al. (1996), in view of DeMatteo et al. (1997), and further in view of Bakker et al. (1999) be withdrawn.

All rejections having been addressed, it is respectfully submitted that the application is in order for allowance, and Notice to that effect is respectfully requested.

Respectfully submitted,

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